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Maria Jose Fernandez

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW

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EXAMINER

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



## DETAILED ACTION

Applicants' arguments and amendments, filed October 13, 2009, have been fully considered but they are not deemed to be fully persuasive. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

### ***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

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were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1 – 3, 5 – 7, 10 – 17 and 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Koll et al. (US 6,346,274) in view of Soppimath et al. (J Controlled Release 2001). This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed June 12, 2009 and those set forth below.

Applicants traverse this rejection on the grounds that Koll would not have been taken into account by one of ordinary skill in the art as this reference would dissuade the skilled artisan from using a polyoxyethylene-derived copolymer such as a poloxamer in the formulation of nanoparticles. The use of Pluronic (a poloxamer) as an additive increases aggregation and also increases the occurrence of deformed particles, in contrast to other additives such as cyclodextrin. One of skill in the art would logically avoid use of polyoxyethylene-derived copolymers in favor of other polymeric reagents. The secondary reference Soppimath is a general review describing different techniques but there is no suggestion or any basis in this document about the specific components, amounts and steps recite in amended claim 1. Soppimath is silent about the dissolution in the organic phase of a biodegradable polymer together with a poloxamer or poloxamine. The combination of Koll and Soppimath provides no derivative basis for the

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method of applicant's invention or the compositions produced by the claimed methodology.

These arguments are unpersuasive. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). (MPEP 2123). Koll discloses that additives are present in amounts ranging from 1% - 20% by weight relative to the total amount of microparticles (col 8, ln 25 – 26). In Table 1, 0.5% by weight of either PLURONIC® F68 or F127 lowered aggregation and that amounts of at least 4% of PLURONIC® F127 increased the amount of deformed particles. No mention is made in regards to the effects of such levels of PLURONIC® F68, which has different properties (e.g., HLB value) that might not cause a higher amount of deformed particles at that level. “[T]he prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed....” *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). **MPEP 2123**, emphasis added. The range of values disclosed by Koll et al., assuming the only other ingredient is the biodegradable polymer in this layer, fall within the range claimed by Applicant. 80% biodegradable polymer with 20% additive is a ratio 1:0.25 while 90% biodegradable polymer with 10% additive would be a ratio of 1:0.11. The instant claims do not exclude nanoparticles that aggregate and/or are deformed. Even if particles aggregate, the individual particles within the aggregate would have a size of less than 1 µm as required by the instant claims. Thus, based on

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the teachings of Koll, one of ordinary skill would not be dissuade from using polyoxyethylene-derived block copolymer additives over other additives such as cyclodextrins.

The teaching of dissolving both the biodegradable polymer and the poloxamer or poloxamine in the nonpolar organic solvent is taught by the primary reference of Koll and does not need to be taught by the secondary reference of Soppamith et al.

5. Claims 1 – 16 and 18 – 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Koll et al. and Soppimath et al. further in view of Levy et al. (WO 96/20698). This rejection is MAINTAINED for the reasons of record set forth in the Office Action mailed June 12, 2009 and those set forth below.

Applicant traverses this rejection on the grounds that Levy discloses the preparation of nanoparticles wherein poloxamers/poloxamines are used as surface modifying agents that are incorporated in the surface of nanoparticles by physical adsorption after the nanoparticles have been formed. This teaching provides no basis from which one of ordinary skill would dissolve such ingredients with a biodegradable polymer in a nonpolar organic solvent as an initial step towards the formation of nanoparticles, teaching away from applicant's claimed methodology. The process results in nanoparticles in which the poloxamine or poloxamer is located in the core of the nanoparticle and not on the surface.

These arguments are unpersuasive. The dissolving of the biodegradable polymer with the poloxamer step is combined with the nonpolar organic solvent is taught by Koll

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et al. As explained at p 12 – 13 of the June 12, 2009 Office Action, Levy is cited for its teachings of the interchangeability of the PLGA polymers with other biodegradable, biocompatible polymers such as polycaprolactone and polyanhydrides (p 7, ln 17 – 20) as well as the interchangeability of the poloxamers (PLURONIC® products) taught by both Levy et al. and Koll et al. with poloxamines (TETRONIC® products), which are only taught by Levy et al.

It is noted that with the exception of claim 19, the methods of preparing and product claims of the present application use the open language of "comprising". Thus, the claims do not exclude a particle as taught by Koll containing the poloxamer or poloxamine dissolved in the nonpolar organic solvent prior to mixing to form particles, to which were added additional surface modifiers such as is taught by Levy. Applicants have also not presented any evidence as to the difference(s) the nanoparticles produced by the instant claimed method and the products of the cited prior. Due to the properties of poloxamer or poloxamine, these molecules could form a layer at the interface between the nonpolar organic solvent and the polar phase when mixed, resulting in microparticles with a polymeric core with the poloxamer or poloxamine adhered to the surface even when the method of the instant claims is used. Arguments without factual support are mere allegations and are not found to be persuasive. As to claim 19, while the no additional steps beyond those explicitly listed can be included in the method, the compositions utilized in steps (a) and (b) are not limited to only the elements listed. \*\*\*

The presenting of an alternative methodology, such as the biodegradable polymer and the PEO-block copolymer not being dissolved in a nonpolar organic solvent by which nanoparticles might be obtained, does not rise to the level of teaching away (MPEP 2123).

6. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koll et al (US 6,346,274) in view and Gref et al. (US 5,543,158).

Koll et al. discloses microparticles of a biodegradable polymer matrix and a polypeptide active ingredient (abstract; col 3, ln 56 – 67). These particles are produced by a process in which the polymers are dissolved in dichloromethane, used by Applicant as a nonpolar organic solvent, and the active ingredient EPO, an active molecule with therapeutic properties, that is dissolved in an aqueous phase which is dispersed in the organic solvent used in step (a); the aqueous (polar) phase and the nonpolar polymer solutions are mixed using stirring to produce an emulsion (example 1, col 8, ln 13 – 31). The polymers used comprise both lactic acid and glycolic acid blocks (col 3, ln 56 – 61). The emulsion is added to another aqueous solution and then the dichloromethane phase is evaporated and the particles are isolated by suction filtration (col 8, ln 31 – 40). Additives can be included in the composition (1% to 20% by weight relative to the total amount of microparticles; col 8, ln 24 – 26). Suitable additives include the polyoxyethylene derived block co-polymers PLURONIC® F68 (MW – 8,400) and F127 (MW = 12,600; Tables 1 and 2, col 9 – 10).



Koll et al. does not explicitly disclose the size of the particles produced using this process or the use of an ethanol and water polar phase.

Gref et al. discloses the preparation of nanoparticles in which the substance to encapsulated with the block copolymer and a block copolymer are mixed and then precipitating the mixture from a solvent system to produce particles in which the hydrophobic moieties of the copolymer are in the core of the particle and the hydrophilic poly(alkylene glycol) moieties are on the surface of the particle (col 13, ln 25 – 30). While a solvent such as ethyl acetate or methylene chloride (dichloromethane) can be used for the block copolymer and substance to be delivered, nanoparticles results form the formation of an emulsion with distilled deionized water (col 13, ln 31 – 37). Alternatively, acetone, methanol or ethanol or their aqueous solutions (e.g., an ethanol and water polar phase) can be used in place of the distilled deionized water (col 13, ln 51 – 53). The use of such solvents will result in a lower concentration of poly(alkylene) units on the surface but would be suitable if a copolymer or second polymer, such as an polyanhydride, that is water sensitive is present in the nanoparticles (col 13, ln 54 – 57). Larger amounts of poly(alkylene glycol) moieties on the surface of the nanoparticles increases the circulating half life of these particles when they are administered (col 2, ln 57 - 59). In example 2, a polylactic co-glycolic acid polymer with PEG groups attached are used (col 10, ln 30 – 50), which reads on a polylactic-co-glycolic acid polymer.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare particles as disclosed by Koll et al. and to use a mixture of ethanol and water as the polar phase. One of ordinary skill would have been motivated

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to do so and reasonably would have expected success as both Koll et al. and Gref et al. teach the production of biodegradable nanoparticles by solvent evaporation processes and the selection of the material used in polar phase will alter the amount of poly(alkylene glycol) on the surface of the particles, that will vary the clearance behavior of the nanoparticles when injected (the *in vivo* half-life). Varying the overall size of the particles will affect the release characteristics and the amount of drug that can be contained within the particles. Optimization of such parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal size and amount of poly(alkylene glycol) groups on the surface of the particles in order to best achieve the desired results relating the *in vivo* drug delivery behavior of the nanoparticles.

### ***Conclusion***

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Jake M. Vu/

Primary Examiner, Art Unit 1618

NMW